PROPRANOLOL, ANXIETY AND THE CENTRAL NERVOUS SYSTEM

Anxiety is characterized by unreasonable feelings of fear, tension and panic, associated with impairment of concentration and insomnia. Almost invariably there are physical disturbances—palpitations, tremulousness, sweating, diarrhoea, etc.—due principally to overactivity of the autonomic, particularly the sympathetic, nervous system, and to increased output of catecholamines by the adrenal medulla.

Most anxiolytic drugs (e.g. barbiturates and benzodiazepines) have important central actions and little or no effect on peripheral structures, consistent with evidence that anxiety depends on activity within the CNS and particularly within the limbic system (the amygdala, hypothalamus and connecting structures). In recent years, however, interest has grown in the use of drugs to relieve the somatic manifestations by blocking the peripheral effects of autonomic discharge, and a number of controlled studies have now been published indicating that propranolol and other adrenergic β-adrenoceptor blocking agents are of value in the treatment of anxiety (Granville-Grossman & Turner, 1966; Bonn, Turner & Hicks, 1972; Tyrer & Lader, 1973; Tyrer & Lader, 1974a) and in inhibiting the physiological response to emotional arousal (Taggart, Carruthers & Somerville, 1973). Similar reasoning forms the basis for the use of propranolol in hyperthyroidism; many of its manifestations are relieved by the drug, although thyroid function is not affected (Turner, Granville-Grossman & Smart, 1965; Shanks, Hadden, Lowe, McDevitt & Montgomery, 1969).

β-adrenoceptor blocking drugs undoubtedly relieve those manifestations of anxiety which are due to stimulation of peripheral β-receptors, and certainly the strongest indication for their use in anxiety is where the patient is troubled by prominent somatic symptoms (Granville-Grossman & Turner, 1966; Imhof & Brunner, 1970; Marsden, 1971; Tyrer & Lader, 1974a). Indeed, where there are few complaints of physical distress, they are probably of little value (Tyrer & Lader, 1974a). However, some investigators have reported that the mental state is also benefited (Nordenfelt, 1965; Frohlich, Dustan & Page, 1966; Frohlich, Tarazi & Dustan, 1969; Suzman, 1971) and there is some current controversy as to the nature of the mechanism responsible for this improvement. On the one hand it is argued that propranolol penetrates the brain, and has sedative effects in animals (Leszkovszky & Tardos, 1965; Bainbridge & Greenwood, 1971), and that it is this central action which is responsible for the amelioration of anxiety. But against this view are various observations in favour of an alternative hypothesis, that the relief of subjective anxiety is entirely dependent on the control, by peripheral β-adrenoceptor blockade, of the physical distress. Thus, the (+)-isomer of propranolol, which has very much less β-adrenoceptor blocking activity than the racemic preparation, does not relieve anxiety (Bonn & Turner, 1971), while practolol, although crossing the blood-brain barrier with difficulty, is effective (Bonn *et al.*, 1972). It is of some relevance that no such controversy exists about the mode of action of propranolol in hyperthyroidism, although there is very good evidence that it improves the mental state (Shanks *et al.*, 1969) even when the patient is psychotic (Granville-Grossman, 1971).

Studies on human subjects have shown no consistent sedative action of propranolol. Dunleavy, Maclean & Oswald (1971) have reported that propranolol in a single dose of 120 mg does not affect the sleep of subjects monitored by continuous EEG recording, while Lader & Tyrer (1972), who used a wide range of tests of psychomotor function, and who also analysed the EEG responses evoked by auditory stimuli and who noted the ratings of mood and bodily symptoms made by their subjects, demonstrated no central effect of either propranolol or sotalol in normal individuals. Bryan, Efiong, Stewart-Jones & Turner (1974) however have observed some increase of reaction time and impairment of hand-eye coordination in normal subjects receiving propranolol.

In two papers by Tyrer & Lader in this issue of the journal, further convincing evidence is given that propranolol, in contrast to diazepam, has no central actions relevant to the relief of anxiety. In the first paper (Tyrer & Lader, 1974b), the authors demonstrate that normal subjects exposed to anxiety-provoking situations are not affected (apart from peripheral β-adrenoreceptor blockade) by either (+)-propranolol or (±)-propranolol, whereas diazepam both reduces subjective anxiety and produces EEG changes characteristic of drug-induced sedation. In the second investiga-

tion (Tyrer & Lader, 1974c), patients with chronic anxiety were studied and again no evidence of any central action of propranolol could be detected even in those subjects whose condition was benefited by the drug; in contrast, diazepam consistently showed clear central effects.

Thus it seems that the sedative effects of propranolol demonstrated in animals are almost certainly irrelevant in the treatment of anxiety, but there is still some doubt about the existence of important central actions other than sedation. Estler & Ammon (1967, 1971) found that the effects of methamphetamine on the motor activity and on the cerebral carbohydrate metabolism of mice were antagonized by propranolol (but it is notable that Dunleavy *et al.* (1971) have reported that propranolol has no effect in human subjects on dexamphetamine-induced sleep disturbances), while Connor, Rossi & Baker (1967) and Srivastava, Kulshrestha, Singh & Bhargava (1973) showed that propranolol introduced directly into the brain of experimental animals inhibits the central effects of catecholamines, suggesting the existence of central β-adrenoreceptors. There is also some indication that propranolol may have a direct effect on the human brain: patients taking it sometimes develop hallucinations (Zacharias, 1971), while Massara & Camanni (1972) have demonstrated that hypthalamic β-adrenoceptors seem to be involved in human growth hormone secretion. Further research to determine the existence and function of β-adrenergic receptors in the brain is clearly indicated, and certainly propranolol will play an important role in these investigations.

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References

BAINBRIDGE, J.G. & GREENWOOD, D.T. (1971). Tranquillizing effects of propranolol demonstrated in rats. *Neuropharmacology*, **10**, 453-458.

BONN, J.A. & TURNER, P. (1971). D-propranolol and anxiety. *Lancet*, **i**, 1355-1356.

BONN, J.A., TURNER, P. & HICKS, D.C. (1972). β-adrenergic receptor blockade with practolol in treatment of anxiety. *Lancet*, **i**, 814-815.

BRYAN, P.C., EFIONG, D.O., STEWART-JONES, J. & TURNER, P. (1974). Propranolol on tests of visual function and central nervous activity. *Br. J. clin. Pharmac.*, **1**, 82-84.

CONNOR, J.D., ROSSI, G.V. & BAKER, W.W. (1967). Antagonism of intracaudate carbachol tremor by local injections of catecholamines. *J. Pharmac. exp. Ther.*, **155**, 545-551.

DUNLEAVY, D.L.F., MACLEAN, A.W. & OSWALD, I. (1971). Debrisoquine, guanethidine, propranolol and human sleep. *Psychopharmacologia (Berl.)*, **21**, 101-110.

ESTLER, C.-J. & AMMON, H.P.T. (1967). The influence of propranolol on the methamphetamine-induced changes of cerebral function and metabolism. *J. Neurochem.*, **14**, 799-805.

ESTLER, C.-J. & AMMON, H.P.T. (1971). Modification by two β-adrenergic blocking drugs of the effects of methamphetamine on behaviour and brain metabolism of mice. *J. Neurochem.*, **18**, 777-779.

FROHLICH, E.D., DUSTAN, H.P. & PAGE, I.H. (1966). Hyperdynamic β-adrenergic circulatory state. *Arch. intern. Med.*, **117**, 614-619.

FROHLICH, E.D., TARAZI, R.C. & DUSTAN, H.P. (1969). Hyperdynamic β-adrenergic circulatory state. Increased β-receptor responsiveness. *Arch. intern. Med.* **123**, 1-7.

GRANVILLE-GROSSMAN, K.L. (1971). *Recent Advances in Clinical Psychiatry*, pp. 212-217. London: Churchill.

GRANVILLE-GROSSMAN, K.L. & TURNER, P. (1966). The effect of propranolol on anxiety. *Lancet*, **i**, 788-790.

IMHOF, P. & BRUNNER, H. (1970). The treatment of functional heart disorders with β-adrenergic blocking agents. *Postgrad. med. J.*, Nov. suppl., 96-99.

LADER, M.H. & TYRER, P.J. (1972). Central and peripheral effects of propranolol and sotalol in normal human subjects. *Br. J. Pharmac.*, **45**, 556-560.

LESZKOVSZKY, G. & TARDOS, L. (1965). Some effects of propranolol on the central nervous system. *J. Pharm. Pharmac.*, **17**, 518-519.

MARSDEN, C.W. (1971). Propranolol in neurocirculatory asthenia and anxiety. *Postgrad. med. J.*, **47**, 100-103.

MASSARA, F. & CAMANNI, F. (1972). Effect of various adrenergic receptor stimulating and blocking agents on human growth hormone secretion. *J. Endocr.*, **54**, 195-206.

NORDENFELT, O. (1965). Orthostatic ECG changes and the adrenergic β-receptor blocking agent, propranolol (Inderal). *Acta med. scand.*, **178**, 393-401.

SHANKS, R.G., HADDEN, D.R., LOWE, D.C., McDEVITT, D.G. & MONTGOMERY, D.A.D. (1969). Controlled trial of propranolol in thyrotoxicosis. *Lancet*, **i**, 993-994.

SRIVASTAVA, R.K., KULSHRESTHA, V.K., SINGH, N. & BHARGAVA, K.P. (1973). Central cardiovascular effects of intracerebroventricular propranolol. *Eur. J. Pharmac.*, **21**, 222-229.

SUZMAN, M.M. (1971). The use of β-adrenergic blockade with propranolol in anxiety syndromes. *Postgrad. med. J.*, **47**, 104-107.

TAGGART, P., CARRUTHERS, M. & SOMERVILLE, W. (1973). Electrocardiogram, plasma catecholamines and

lipids, and their modification by oxprenolol when speaking before an audience. *Lancet*, **ii**, 341-346.

TURNER, P., GRANVILLE-GROSSMAN, K.L. & SMART, J.V. (1965). Effect of adrenergic receptor blockade on the tachycardia of thyrotoxicosis and anxiety state. *Lancet*, **ii**, 1316-1318.

TYRER, P.J. & LADER, M.H. (1973). Effects of beta adrenergic blockade with sotalol in chronic anxiety. *Clin. Pharmac. Ther.*, **14**, 418-426.

TYRER, P.J. & LADER, M.H. (1974a). Response to propranolol and diazepam in somatic and psychic anxiety. *Br. med. J.*, **2**, 14-16.

TYRER, P.J. & LADER, M.H. (1974b). Physiological and psychological effects of ±-propranolol, +-propranolol and diazepam in induced anxiety. *Br. J. clin. Pharmac.*, **1**, 379-385.

TYRER, P.J. & LADER, M.H. (1974c). Physiological response to propranolol and diazepam in chronic anxiety. *Br. J. clin. Pharmac.*, **1**, 387-390.

ZACHARIAS, F.J. (1971). Propranolol in hypertension: a 5 year study. *Postgrad. med. J.*, **47**, 75-79.